BILLING CODE: 4140-01-P

DEPARTMENT: DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Government-Owned Inventions; Availability for Licensing

AGENCY: National Institutes of Health.

ACTION: Notice.

SUMMARY: The invention listed below is owned by an agency of the U.S. Government and is available for licensing and/or co-development in the U.S. in accordance with 35 U.S.C. 209 and 37 CFR part 404 to achieve expeditious commercialization of results of federally-funded research and development. Foreign patent applications are filed on selected inventions to extend market coverage for companies and may also be available for licensing and/or co-development.

ADDRESSES: Invention Development and Marketing Unit, Technology Transfer Center, National Cancer Institute, 9609 Medical Center Drive, Mail Stop 9702, Rockville, MD, 20850-9702.

FOR FURTHER INFORMATION CONTACT: Information on licensing and co-development research collaborations, and copies of the U.S. patent applications listed below may be obtained by contacting: Attn. Invention Development and Marketing Unit, Technology Transfer Center, National Cancer Institute, 9609 Medical Center Drive, Mail Stop 9702, Rockville, MD, 20850-9702, Tel. 240-276-5515 or email ncitechtransfer@mail.nih.gov. A signed Confidential Disclosure Agreement may be required to receive copies of the patent applications.

SUPPLEMENTARY INFORMATION: Technology description follows.

Title of invention:

Small Molecule Inhibitors of Drug Resistant Forms of HIV-1 Integrase

Description of Technology:

Integrase strand transfer inhibitors ("INSTIs") are currently in use as a component of prophylactic antiretroviral therapy for preventing HIV-1 infection from progressing to AIDS. Three INSTIs are approved by the FDA for inclusion in antiretroviral regiments: raltegravir (RAL), elvitegravir (EVG) and dolutegravir (DTG). Clinicians have already identified several HIV-1 integrase mutations that confer resistance to RAL and EVG, and additional mutations that confer resistance to all three INSTIs has been identified in the laboratory.

Researchers at the National Cancer Institute discovered small-molecule compounds containing 1-hydroxy-2-oxo-1,8-naphthyridine moieties whose activity against HIV-1 integrase mutants confer resistance to currently approved INSTIs. These new compounds exhibit potent and selective activity against comprehensive and varied panels of INSTI-resistant mutants of HIV-1 integrase. Preliminary rodent efficacy, metabolic, and pharmacokinetic studies have been completed by the NCI researchers.

The National Cancer Institute (NCI) seeks partners to in-license or co-develop this class of compounds for therapeutic use. Parties interested in licensing the technology should submit an Application for Licensing, and seek detailed information from the Licensing and Patenting Manager indicated below.

Co-development partners would apply under a Cooperative Research and Development (CRADA) to conduct pre-clinical studies that include lead optimization, *in vitro* and *in vivo* evaluation and preclinical development of a novel series of INSTIs for the treatment

of infection by HIV-1 strains with resistance to currently available integrase inhibitors, including raltegravir and elvitegravir. Under the CRADA, further *in vitro* and *in vivo* ADME, as well as activity studies, will be conducted by the partner on current and optimized lead compounds using rodent and non-rodent models. Efficacy studies in non-human primates of select compounds are needed and will be part of the CRADA program. The CRADA scope will also include all aspects of toxicity studies, and synthesis scale up under GMP of optimized lead compounds to support submission of a successful IND application.

Interested potential CRADA collaborators can receive detailed information by contacting the Licensing and Patenting Manager (see below). Interested parties will receive detailed information on the current status of the project after signing a confidentiality disclosure agreement (CDA) with NCI. Interested candidate partners must submit a statement of interest and capability to the NCI point of contact for consideration by 5:00pm Eastern Standard Time, December 30, 2016.

Guidelines for the preparation of a full CRADA proposal will be communicated to all respondents with whom initial confidential discussions have been established. Licensing of background technology related to this CRADA opportunity, specifically HHS Reference No.: E-093-2013/0,1,2, entitled "Compounds for Inhibiting Drug-Resistant Strains of HIV-1 Integrase", is also available to potential collaborators. All proposals received by the above date will be considered. NCI reserves the right to consider additional proposals or none at all if no partner is selected from the initial response. Further information about the NCI Technology Transfer Center can be found on its web site http://techtransfer.cancer.gov.

Potential Commercial Applications:

- HIV therapeutic for drug-resistant compounds of HIV-1 integrase

Value Proposition:

- Currently, the only INSTI effective against drug resistant mutants of HIV-1 integrase

Development Stage:

Pre-clinical (in vivo validation)

Inventor(s):

Terrence Burke, Stephen Hughes, Yves Pommier, Xue Zhao, Mathieu Metifiot, Stephen Smith, Barry Johnson, Christophe Marchand (all from NCI)

Intellectual Property:

HHS Reference No.: E-093-2013/0,1,2; all entitled "Compounds For Inhibiting Drug-Resistant Strains Of HIV-1 Integrase"

US Provisional App. No.: 61/952,928 filed May 16, 2013

US Provisional App. No.: 61/899,061 filed November 1, 2013

International App. No.: PCT/US2014/037905 filed May 13, 2014

Brazilian App. No.: BR1120150287603 filed May 13, 2014

Canadian App. No.: CA2912064 filed May 13, 2014

Chinese App. No.: 2014-80039611.5 filed May 13, 2014

European App. No.: 14728395.6 filed May 13, 2014

Indian App. No.: 3937/KOLNP/2015 filed May 13, 2014

Japanese App. No.: JP100078282 filed May 13, 2014

US Non-Provisional App. No.: 14/891,309 filed May 13, 2014

South African App. No.: ZA2015/08408 filed May 13, 2014

Publications:

Zhao, X.Z. *et al*., "HIV-1 Integrase Strand Transfer Inhibitors with Reduced Susceptibility to Drug Resistant Mutant Integrases", ACS Chem Biol., Apr 15, 2016, 11(4):1074-81.

Métifiot, M. *et al*.., "Selectivity for strand-transfer over 3'-processing and susceptibility to clinical resistance of HIV-1 integrase inhibitors are driven by key enzyme-DNA interactions in the active site", Nucleic Acids Res., Aug 19, 2016, 44(14):6896-906.

Zhao, X. Z. *et al*., "4-Amino-1-hydroxy-2-oxo-1,8-naphthyridine-containing compounds having high potency against raltegravir-resistant integrase mutants of HIV-1", *J. Med. Chem.*, *57*, 5190-5202 (2014), Doi: 10.1021/jm501059k

Zhao, X. Z. *et al*., "Bicyclic 1-hydroxy-2-oxo-1,2-dihydropyridine-3-carboxamide-containing HIV-1 integrase inhibitors having high antiviral potency against cells harboring raltegravir-resistant integrase mutants", *J. Med. Chem.*, *57*, 1573-1582 (2014), Doi: 10.1021/jm401902n

Contact Information:

Requests for copies of the patent application and inquiries about licensing, research collaborations, and co-development opportunities for this invention should be sent to Lauren Nguyen-Antczak, Ph.D., J.D., Senior Licensing & Patenting Manager, NCI Technology Transfer Center, 8490 Progress Drive, Suite 400, Frederick, MD 21701, Tel: (301) 624-8752, email: lauren.nguyen-antczak@nih.gov.

Dated: October 25, 2016.

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John D. Hewes

Technology Transfer Specialist, Technology Transfer Center, National Cancer Institute

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